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10/590,808	01/12/2007	Rob Hooft Van Huijsduijnen	294685US0PCT	2174

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EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,808	HOOFT VAN HUIJSDUIJNEN ET AL.	
	Examiner	Art Unit	
	WALTER E. WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/25/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101 and 112, second

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 provide for a method of using a methylene amide derivative, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-19 are also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, Applicant discloses a method of using a methylene amide **derivative** of Formula (I), where the compounds have "substituted" thienyl or "substituted" phenyl groups.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See. E.g., *In re Wilder*, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as "derivative" or "substituted" used herein), however, may not suffice to meet the written description requirement. This is particularly true

when a compound is claimed in purely functional terms. See *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid form others having the same activity or function. A description of what a material does, rather that of what it is, usually does not suffice. . . . The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of a genus, which features constitute a substantial portion of the genus. See *Univ. of Calf. v. Eli Lilly*, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not specifically define what constitutes a representative number of species, the courts have indicated what des not constitute same. See, e.g., *In re Gostelli*, 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989), holding that the disclosure of two chemical compounds within a subgenus did not adequately describe such subgenus.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and /or chemical

properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention form other materials and would lead one f skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

The present disclosure fails to recite a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation of "derivative" or "substituted" such that the artisan would readily identify the scope of this active agent. Because there is no support for "derivative" or "substituted" in the specification, it is not clear that applicant had possession of the claimed invention at the time of filing.

Enablement Rejection

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for treating or preventing chronic heart failure, endothelial dysfunction, or cardiovascular disorders in general.

1) Scope of active agents

The specification does not adequately enable a person having ordinary skill in the art to use the claimed invention in light of the scope of methylene amide derivatives claimed, which have a plethora of functional groups including a vast range of heteros. It is not clear from the specification which compound of formula I was tested in the chronic heart failure model or how results obtained therewith can be extrapolated to be expected for the full scope of the compounds claimed, which are inclusive of many structurally diverse species. There is no reasonable basis for assuming that myriads of compounds not made and thus not tested will share the requisite minimum activity needed to practice the invention. See In re Fisher, 166 USPQ 18, and In re Surrey, 151 USPQ 724 in regards to sufficiency of disclosure in cases directed to structure sensitive arts. The artisan would be faced with the impermissible burden of undue experimentation in determining which compound(s) showed sensitivity in treating a cardiovascular disorder.

2) Prevention of chronic heart failure, endothelial dysfunction, or cardiovascular disorders in general

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2: The claimed invention is drawn to a method of treating or preventing cardiovascular disorders in general, as well as preventing endothelial dysfunction, heart failure and chronic heart failure.

Factors 3 and 7: In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention of cardiovascular disorders in general, as well as preventing endothelial dysfunction, heart failure and chronic heart failure, could be effectively achieved by the administration of the claimed active agent.

As set forth in In re Marzocchi et al., 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in

describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling."

Treatment of chronic heart failure, for example, is well developed (see Sato et al., Medical Science Monitoring 2006), but the state of the art with regard to preventing chronic heart failure is grossly underdeveloped.

In this regard, Sato et al. is cited. Sato et al. discloses that chronic heart failure is a complex syndrome, and that a single biochemical marker cannot reflect its multiple manifestations. Therefore, treating this disease is unpredictable, and as such the artisan would not accept that chronic heart failure, endothelial dysfunction, or cardiovascular disorders in general can be prevented with applicant's claimed compounds. In particular, there is no known agent that is effective against preventing chronic heart failure. The Sato reference clearly shows that for the different causes of ischemic cardiovascular disease and the severity of the disease, there is not one agent or combination therapy thereof that is effective at preventing this disease (see Abstract, and Systemic Markers at pg. 2-4).

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP

§2164.02). However, in light of the state of the art, there is no apparent disclosure to support the contention that the prevention of chronic heart failure, endothelial dysfunction, or cardiovascular disorders in general can be achieved as claimed by applicant.

Factor 4: Applicant also disclosed how a human or animal might be administered this composition. Applicant did not disclose, for example, a protocol or guidance as to how prevention cardiovascular disorders in general, as well as endothelial dysfunction, heart failure and chronic heart failure could be achieved. Applicant's disclosure is inadequate as to directing or guiding how the proposed agents can be employed to accomplish such objectives in a predictable manner.

Factor 5: The specification at pages 40-41 provides evidence demonstrating that a compound of formula I restores dilation in murine arteries *in vitro*. While the present claims encompass preventing cardiovascular disorders in general, as well as preventing endothelial dysfunction, heart failure and chronic heart failure, Applicant's data merely establishes a treatment of murine arteries *in vitro*.

Factor 6: The burden of preventing chronic heart failure, endothelial dysfunction, or cardiovascular disorders in general with the claimed compound is much greater than that of treating chronic heart failure or inhibiting endothelial dysfunction, with a specific compound. Since the present specification would not enable the skilled artisan to prevent these diseases or treat any cardiovascular disorder with the claimed compound,

a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the full scope of the presently claimed invention.

Factor 8: In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

3)Scope of the diseases being treated

Given the unpredictable nature of treating chronic heart failure cited in the art above, one of ordinary skill in the art would not accept on its face that applicant's claimed active agent could treat cardiovascular disorders in general. The artisan would be subject to undue experimentation in determining which type of a cardiovascular disorder showed some sensitivity to a compound of formula I in order to have a reasonable expectation of success in treating the disorder.

Furthermore, applicants have not shown how endothelial dysfunction or chronic heart failure can be treated with a compound of formula I. The working example shows *in vitro* incubation of murine arteries with {{4-[94-hexylphenyl)ethybenzyl}[4-9trifluoromethyl)benzyl]amino}(oxo)acetic acid. No scientific basis exists for treating this as a method for treating endothelial dysfunction or chronic heart failure *in vivo*. Given the unpredictable nature in treating chronic heart failure, applicant's disclosure is inadequate for enabling the artisan to treat endothelial dysfunction or chronic heart failure.

Summary

As the discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that preventing or treating cardiovascular disorders in general, as well as preventing or treating endothelial dysfunction, heart failure and chronic heart failure in a mammal with the claimed compound could be achieved. In order to actually achieve such an objective, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. The skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1-19 are deemed properly rejected.

112 2nd Paragraph Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "derivative" is indefinite since it is not clear at what point a compound becomes sufficiently different from its parent compound to become a "derivative" of the parent.

The Markush groups of where the language begins, "selected from the group consisting essentially of" makes these claims indefinite since a Markush group must contain a closed selection, and "consisting essentially of" permits the inclusion of additional unspecified members. MPEP 803.02 [R-5] sanctions the use of "consisting of".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

For the purpose of this rejection the claims have been construed as an administration of a compound of formula I to a patient.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al., (US 2002/0025126) in view of Hooft van Huijsduijnen et al., (Expert Opinion on Therapeutic Drug Targets 2002.) and in further view of Sowers et al., (Hypertension 2001).

Liu et al. teach the compounds instantly claimed. Liu discloses compounds of Formula I, wherein RI=CH2Ph, R2a and R2b=H and Cy=phenyl substituted with phenyl (see Example 30, at pg. 18). Liu also discloses compounds of Formula I, wherein RI=CH2CH2Ph, R2a and R2b=H and Cy=phenyl substituted with -O-CH2-quinoline (see Example 11, at pg. 15). Liu also teaches that these compounds are protein tyrosine kinase PTP1B inhibitors useful in treating autoimmune diseases, acute and chronic inflammatory diseases, osteoporosis, obesity, cancer, malignant diseases, and type I and type II diabetes. (See abstract and [0227].)

Liu et al. differs from the instant claims insofar as it does not teach that the disease can be cardiovascular disorders, endothelial disfunction, heart failure or chronic heart failure.

Hooft van Huijsduijnen et al. teach that PTP1B inhibitors are useful in treating inflammation and therefore vascular leakage, an endothelial dysfunction, by inhibiting PTP-β. (See Vascular Leakage at pg. 640.)

Sowers et al. teach that cardiovascular diseases, including heart failure, are a major cause of mortality in persons with diabetes. (See abstract and HOPE trial at pg. 1055.)

It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to administer the compounds of Liu for the treatment of cardiovascular disorders, endothelial dysfunction, heart failure and chronic heart failure since these diseases are associated with diabetes. A person taking these compounds for diabetic purposes would inevitably be treating cardiovascular disorders and endothelial leakage.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
Patent Examiner
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/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612